MULTILAYER TABLET: A NEW TREND IN SOLID DOSAGE FORMS

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ABSTRACT
Pharmaceutical products that are designed for oral delivery are currently available mostly in the immediate-release type. These are designed for immediate release of drug and rapid absorption. For added advantages of therapy and enhanced efficacy sustained and controlled release formulations are being used more and more. These forms also offer the advantage of patient compliance. Several advantages over the conventional are seen but still some problems arises in preparation of this kind of dosage form such as physical incompatibility, chemical incompatibility etc. Therefore the bilayer and multilayer tablets are known as a novel drug delivery system. Multilayered tablets possess various benefits, namely the ability to prevent incompatibility between drugs and Excipients; and by providing multiple release kinetics profiles in single delivery system of either the same or different drugs, by means of different release control mechanisms. The aim of this article is to review multilayered tablet dosage forms and outline its advantages. Various factors governing the design and evaluation of these types of tablets have also been discussed.

Keywords: Sustained drug delivery, Controlled drug delivery, multilayered tablets, Novel drug delivery system.
INTRODUCTION
Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage forms. The reasons that the oral route achieved such popularity may be in part attributed to its ease of administration as well as the traditional belief that by oral administration the drug is as well absorbed as the foodstuffs that are ingested daily. In fact, the development of a pharmaceutical product for oral delivery, irrespective of its physical form (solid, semisolid, or liquid dosage form), involves varying extents of optimization of dosage form characteristics within the inherent constraints of gastrointestinal (GI) physiology.[1]

Problems related with conventional drug delivery system are:

- Poor patient compliance.
- Improved chances of missing the dose of a drug with short half-life for which repeated administration is necessary.
- The unavoidable fluctuations of drug concentration may lead to under medication or over medication.
- A typical peak-valley plasma concentration time profile is obtained which makes attainment of steady-state condition difficult.
- The fluctuations in drug levels may lead to precipitation of adverse effects especially of a drug with small Therapeutic Index whenever over medication occur.[2]
- However, patient compliance is likely to be poor when patients need to take their medication three to four times daily on chronic basis. Thus, these shortcomings have been circumvented with the introduction of controlled release dosage forms.

Pharmaceutical products designed for oral delivery and currently available on the prescription and over-the-counter markets are mostly the immediate-release type, which are designed for immediate release of drug rapid absorption. Because of their clinical advantages over immediate-release pharmaceutical products containing the same drugs, sustained-release pharmaceutical products, such as those formulated on the basis of spansule coating technology, have over the past decade gradually gained medical acceptance and popularity since their introduction into the marketplace. Recently, a new generation of pharmaceutical products, called controlled-release drug delivery systems, such as those developed from the osmotic pressure-activated drug delivery system, have recently received regulatory approval.
for marketing, and their pharmaceutical superiority and clinical benefits over the sustained-release pharmaceutical products have been increasingly recognized.\textsuperscript{[2]} Through such dosage forms several advantages over the conventional are seen but still some problems arises in preparation of this kind of dosage form such as physical incompatibility, chemical incompatibility etc. Therefore the bilayer and multilayer tablets are known as a novel drug delivery system.

**Zero order sustain release**

It comprises either a hydrophilic or hydrophobic intermediate layer containing the active drug or one or two barrier layers which are press coated to the faces of the tablet core, leaving the sides of the core exposed. Many authors have evaluated this design. \textsuperscript{[3]} The widely used barrier polymers for sustaining the drug delivery are either hydrophilic and/or hydrophobic materials. In general linear release profiles can be obtained by applying hydrophilic barrier layers on both the faces of a hydrophobic matrix tablet or by applying a hydrophilic barrier layer on one face and hydrophobic barrier layer on the other face of the matrix tablet. However, net formulation and variables within the matrix and barrier layers is important to be controlled rather carefully in order to achieve zero-order drug release from hydrophobic matrix tablet coated with hydrophobic barrier layers on both the faces.

**Time Programmed Delivery System**

Time programmed followed by time controlled release, when the delivery of drug is required in a time controlled fashion in the gut, rather than release of drug in continuous manner according to circadian rhythm. This system consists of core which is coated with different polymeric barriers. The release of drug from the core tablet after swelling or after eroding of hydrophobic or hydrophilic barrier of coating that show pulsatile release of the drug followed by extended or prolonged release of the drug delivery system provides immediate release of the drug. \textsuperscript{[4, 5]}

**Bimodal Release Profile**

Bimodal release profile show an initial rapid release followed by slow release and again a second phase of rapid drug release i.e. sigmoidal release profile. This system compensates the slow absorption in the stomach and small intestine and for programmed pulse releases that perform more effectively at the site of action to undertake periodic changes. \textsuperscript{[6, 7]}
Quick/Slow Delivery System

Quick/slow delivery system which is characterised by initial rapid release achieves therapeutic effect immediately sustains a constant release of drug to maintain plasma level concentration. This concept applied in cases where dose regimen does not satisfy simple release of the drug. [8]

MULTILAYER TABLET

There are many reasons for the development of two or more drugs incorporated in single dosage form in several diseases. This concept not only use in case of emergencies but also in common disease like Parkinson, allergic condition etc. [9] The intension behind development of such formulation is that when patient unable to take frequent dosing due to various reasons. [10]

This concept was preferred for combination of different APIs in single dose therefore to get relief in single dose and to attain site therapeutic concentration immediately and also maintain same dose over 12hr. [11] FDCs gaining importance globally which are therapeutically justified and are available in critical disease condition e.g. AIDS, Cancer and Pulmonary disease. Multilayer tablet technology contains two or more APIs being used in treatment of wide range of chronic condition. It is applicable for broad range of compatible as well as incompatible drug for both immediate and sustained release dosage forms. Currently about two-third of all prescriptions are dispensed as solid dosage forms. [12]

Many combinations are available and being used which can provide immediate and modified release of two drugs or dual release rate of same drug in single dosage form by using hydrophilic and hydrophobic polymer matrices. It is therapeutically justified that combination of modified and immediate release matrix found to increase bioavailability. [13] Compaction of different granules in the form of various layer in single tablets are called as multilayer tablets. It generally consists of parallel, clear, coloured, visual distinct layers two to three or more APIs or APIs along with functional or non-functional placebo layers, sometimes to avoid interaction between different incompatible layers. Oral solid multiple drug delivery system in the form of FDCs are beneficial than the other oral formulation.

Three layer tablets are formulated for controlled release, usually consists of drug core layer sandwiched by external layers, which may contains different amount of drug to form a concentration gradient matrix or just act as a barrier layer in order to restrict release or to
minimize burst effect upon in-vivo placement.\textsuperscript{[14]} In the multilayer tablet one swellable layer and one erodible layer whose functions are to control the hydration and swelling rate of the core, and thereby slow down dissolution of the drug.\textsuperscript{[15]} When the tablet comes into contact with gastric juices, it increases considerably in volume and thus remains in the stomach for a longer time.

Multilayered systems which contains bilayered, triple-layered, quadruple-layered, etc are becoming increasingly recognized as controlled-release drug delivery systems. Multilayered tablets possess various benefits, namely the ability to prevent incompatibility between drugs and excipient; and by providing multiple release kinetics profiles in single delivery system of either the same or different drugs, by means of different release control mechanisms, immediate drug release using a disintegrating monolithic matrix in order to achieve an initial peak in plasma drug level, delayed drug release rearchieved using an eroding monolithic matrix which may deliver another active drug to the latter part of gastrointestinal tract, controlled release swelling monolithic matrix carry out together swell as well as erode in which drug constantly released and better management control and regulation of release profiles by retarding initial burst release and achieving zero-order kinetics.\textsuperscript{[16]}

Multi-layer tablet dosage forms are designed for a variety of reasons\textsuperscript{[17]}

1. To separate incompatible Active pharmaceutical ingredient (APIs) from each other, to control the release of API from one layer by utilizing the functional property of the other layer.
2. To control the delivery rate of either single or two different active pharmaceutical ingredient.
3. To administer fixed dose combinations of different APIs, prolong the drug product life cycle, fabricate novel drug delivery systems such as chewing device, buccal/ Mucoadhesive delivery systems, and floating tablets for gastro-retentive drug delivery.
4. To modify the total surface area available for API layer either by sandwiching with one or two inactive layers in order to achieve swellable/erodible barriers for modified release.

**Objective of preparing multilayer tablets\textsuperscript{[18-20]}**

1. To use different APIs in combination having proven advantages over single compounds administered separately for therapeutic effect.
2. To overcome the limitations in case of a single drug which is unable to treat or avoid adverse drug effect, if any.
3. To get dual release profile so as to reduce dosing frequency and thereby increasing patient compliance.

4. To combine compatible or incompatible drugs with different release characteristic in same dosage form and enhancing the stability of dosage form as compared to its conventional dosage form.

5. To treat critical disease condition when single active unable to produce complete therapeutic action and to maintain over a period 12 h or more.

**Ideal properties of Multilayer tablets**\(^{[21]}\)

- Drug should not be affected by compaction of each layer and physically stable; and withstand the mechanical shock.
- Separation of layers should not occur during various stages such as compression, coating, packing, shipping and storage.
- Layer should not fuse into non-disintegrating matrix, should have clear, parallel, visual separation in final compressed tablets.
- If it consists of disintegrating matrix, it should be disintegrated within GIT, modified release part should not be affected dissolution profile of IR part and slow and gradual erosion of second layer for slow release of drug.

**TYPES OF MULTILAYER TABLETS**

Bilayer tablets to quadruple layered tablets are available.

1. **BILAYER TABLET**

Bilayer tablets are suitable for sequential and simultaneous release of two different API’s. In this one layer is immediate release and another layer is sustained release act as a maintenance dose. Bilayer tablet is suitable mean of to deliver two drugs at one time without any dynamic and pharmacological interaction.
2. TRIPLE LAYER TABLET
Triple layer tablet consist of three layer of which first layer is for immediate release of drug and the second layer is for sustained release. These two layers are separated with the middle barrier layer. This is more suitable for the delivery of two drugs which have interactions in them.

3. TABLET IN TABLET

4. SURROUNDUNG COATED CORA TABLET
Multilayer Tablet and Controlled Release
Multilayer tablet consists of layers of drug with different release rate, having ability to prevent drug-excipient incompatibility. It provides multiple release kinetics profile in single delivery system of one or more drugs. In this immediate release and then sustained release of drug is designed as control system. Immediate release layer is designed with disintegrating monolithic matrix in order to achieve initial peak and sustained release layer is designed with erodible monolithic matrix to deliver the drug as later part to maintain the drug plasma concentration.

Design of Multi-Layered Tablets\(^{22-24}\)
The design of multi-layer through modulating layers which allows different tablet designs for the production with specific release to achieve different dissolution patterns like bimodal, delayed and multi-modal delivery have been given below:
- Zero order sustained release
- Time programmed delivery system
- Bimodal release profile
- Quick / slow delivery system

Generally the drug release mechanism from hydrophilic, swellable matrices is a coupling of polymer macromolecular relaxation and drug diffusion. Both the phenomena depend initially on the rate at which water may enter the device. Multi layered design is based on the following aspects:
A. Matrix hydration rate and consequent swelling and/or lowering of diffusion rate;
B. Modulation of the surface of matrix through which the drug can be delivered.

**Major advantages of bimodal matrix tablets include** [25]
- Change in release rate upon medium change.
- Applicability to different types of drugs
- Complete dissolution in human body fluids avoiding empty remnants; and
- The possibility to achieve therapeutic blood levels similar to those obtained by administration of two smaller doses over an extended period of time.

**Advantages of the multi-layer tablet dosage form** [26]
- Lighter and compact.
- Flexible Concept.
- Cost is lower compared to all other oral dosage form.
- They are unit dosage form and offer the greatest capabilities of all oral dosage form for the greatest dose precision and the least content variability.
- Easy to swallowing with least tendency for hang-up.
- Objectionable odour and bitter taste can be masked by coating technique.
- Suitable for large scale production.
- Greatest chemical and microbial stability over all oral dosage form.
- Easiest and cheapest to package and strip.

**Disadvantages of Multilayer Tablet Dosage Form** [27]
- Difficult to swallow in case of children and unconscious patients.
- Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.
- Problems during In-process Quality Control (IPQC) such as layer separation during storage, packaging, shipping, insufficient hardness, cross-contamination etc.
- Regulatory aspects that it should be based on believable therapeutic and medical justification which is clinically relevant.
- Set up of bilayer or trilayer tablets is time consuming, take long time to initial setup, speed, and many times problem arise during tableting as compared to single layer conventional tablet press in machine setup, cost and production output.

**Parameters to be considered during Multilayer tableting** [28, 29]
Parameters primarily are considered during multilayer tableting. It is totally depending upon handling and experience of such multi-dosing tablet press.

**Dwell time**
It is the contact between punch head and compression roller. If shorter the first layer-dwell time, which results into pours, aeration, capping and hardness problems. It may be removed the mistakes by reducing the turret-rotation speed or by extending the dwell time.

**Cohesiveness**
When the first layer is compressed at a very high compression force, bonding between layers is severely controlled. Various bilayer formulations necessitate a first layer compression force NMT 3 Kpor 30 N to maintain the ability of first layer to bond with the second layer. Thus at elevated manufacturing speed, the jeopardy of separation and capping increases which can be minimised by adjusting adequate dwell time at all compression stages.

**Risk of separation and capping**
It is necessary to avoid risk of separation and capping, by forming correct bonding which can be attained by the first layer formation at low compression force. Therefore this first layer can still interact with the second layer during final compression of the tablet.

**Cross-contamination**
Multilayer tablet machines are equipped with suction nozzles or dust extractor to remove fine powder or granules to eliminate cross-contamination between the two layers and getting a clear visual separation between layers. It is very important to remove any powder residue from the die plate and for this purpose dedicated scraper plate are located before and after
each die fill, to remove residual powder dust to the outside of the die table, where the high efficiency suction nozzles are located.\[^{30}\]

**Final compression force**

This force is applied on the final bilayer tablet is always more than the compression force on first layer, which results in suitable bonding of both the layers.

**Weight variation**

Weight variation occurs some time due to non-uniform flow of granules, incomplete die filling and lower punch jamming due to excessive fines in final blend and thus these parameters should be controlled carefully during tableting.

**Weight adjustment**

First layer pressure is useful for weight adjustment of second layer. Many formulators use such technique to achieve desired weight instead of using weight adjustment knob that totally depends on handling experience of such double rotary press.

**Hardness and Thickness**

This parameters need to be tightly controlled during final compression because it directly affect the release of active. Many times due to high hardness disintegrating matrix may take time more than limits.

**The manufacturing of multilayered matrix tablets involves the following steps\[^{31-33}\]**

The manufacturing of the matrix core tablets is performed in a separate step and is usually done by using a regular rotator press. Since the barrier layer is important to monitor drug release mechanism, its weight, thickness, and compaction need to be tightly controlled during final compression. The process includes the following steps.

- Dosing of the bottom layer
- Transfer of the prepared core
- Insertion into die
- Dosing of the top layer
- Final compression
- Ejection.

**CONCLUSION**

The design feature of multilayered tablets provides unique product performance objectives
which are otherwise not achievable by conventional tablets, but also brings a new set of challenges for formulation design, manufacturing process, controls and product life performance requirements. In addition to manufacturing science challenges, they also add challenges in establishing relevant regulatory controls to meet the product performance requirements over the life of the drug product. To meet these requirements a higher level of understanding in the ingredients and manufacturing variables is critical to manage the risks associated with product acceptability over the life cycle to avoid batch failures and batch recall.

Thus, the development and production of quality bi-layer tablets require a comprehensive understanding of the product and process in order to address challenges in manufacturing such as accuracy in weight control of each individual layer, de-lamination/layer-separation during manufacturing and storage, insufficient tablet breaking force and cross-contamination between the layers (especially for incompatible APIs). The objective of the dosage form is to ensure that the drugs available to the patient are not only safe and effective, but are also properly manufactured and packaged to meet the established quality target product profile over its shelf life. A well-developed product will effectively address these issues by including appropriate control strategies and establishing the functional relationships of the material attributes and process parameters critical to the multilayer tablet quality.

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